Suitability of polylactide bone plates and screws for fixation of mandibular fractures

Tams, Jan

CHAPTER 3

HIGH-IMPACT POLY(L/D-LACTIDE) FOR FRACTURE FIXATION: *IN VITRO* DEGRADATION AND ANIMAL PILOT STUDY

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SUMMARY

The impact strength of amorphous lactide copolymers can be significantly improved by blending with biodegradable rubbers. Rubber toughening of amorphous poly(85L/15D-lactide) with the copolymer poly(50/50-trimethylenecarbonate-co-ϵ-caprolactone) results in a high-impact polymer (PDLLA/P(TMC-CL)). *In vitro*, the PDLLA/P(TMC-CL) blend retained its tensile and impact strength for a long period of time. Up to 45 weeks, the amount of water absorbed by the blend remained very low and no significant mass loss was observed. To test the suitability for fracture fixation, in a dog study mandibular fractures were fixed with PDLLA/P(TMC-CL) bone plates and screws. Bone healing was uneventful without premature failure of the implants. Although long-term degradation studies have to be carried out, PDLLA/P(TMC-CL) seems to be promising for application in fracture fixation.

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INTRODUCTION

In previous studies we have reported on semi-crystalline as-polymerized poly-(L-lactide) (PLLA) implants for fixation of mandibular and zygomatic fractures.[1-4] The PLLA implants provided enough strength to enable undisturbed bone healing. However, the degradation time of the PLLA implants, which was initially estimated as 12 to 18 months,[5] was unacceptably long. Even after 6 years, the PLLA implants had not been completely degraded and resorbed.[6-8] Other studies confirmed our findings that crystalline remnants of poly(lactide)s show a very low degradation rate.[9-11] A late tissue response was observed in patients with PLLA implants after 3 years, making a removal operation of the remnants of implants necessary.[6,7] The late tissue response might very well be related to the highly crystalline PLLA remnants.[6,7]

To avoid the negative side effects of as-polymerized PLLA, amorphous lactide copolymers are preferred.[12] However, amorphous lactide copolymers have a low impact strength. When mandibular fractures are treated with these implants, there is a risk of screw or plate failure under dynamic loads. The impact strength of amorphous lactide copolymers can be significantly improved by blending with biodegradable rubbers.[13,14] The present study provides the results of the *in vitro* degradation of a blend of amorphous poly(85L/15D-lactide) (PDLLA) with a 20 wt% of 50/50 mol/mol copolymer of trimethylenecarbonate (TMC) and ϵ-caprolactone (CL) (PDLLA/P(TMC-CL)). Normally, upon rubber toughening, the tensile strength and bending modulus of a blend decrease. To establish whether PDLLA/P(TMC-CL) is suitable for fracture fixation, in an animal pilot study the bone healing of mandibular fractures treated with PDLLA/P(TMC-CL) bone plates and screws was studied.

MATERIALS AND METHODS

Preparation and mechanical properties of the PDLLA/P(TMC-CL) blend

Poly(85L/15D-lactide) and poly(50/50-trimethylenecarbonate-co-ϵ-caprolactone) rubber were synthesized according to standard procedures. The preparation of the blend containing 20 wt% rubber has been reported elsewhere.[14] The chemical structures of the monomers are presented in Figure 1. Test specimens, bone plates and screws were compression moulded in stainless steel moulds at 120 °C.The initial tensile properties of the PDLLA/P(TMC-CL) blend were measured according to ASTM D1708 specifications on a Instron 4301 tensile tester at a crosshead speed of 10 mm/min. The impact strength was measured according to DIN 53453 (Dynstat unnotched) and ASTM D256 (Izod notched) specifications on a Zwick pendulum apparatus.

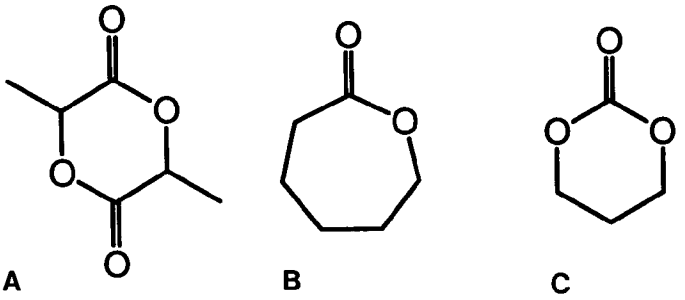

Figure 1 Chemical structures of the monomers:
(A) lactide, **(B)** ϵ-caprolactone and **(C)** trimethylenecarbonate.

In vitro study

The mechanical properties of the PDLLA/P(TMC-CL) blend were monitored *in vitro* up to 45 weeks. For the *in vitro* degradation, PDLLA/P(TMC-CL) test specimens were stored in a phosphate buffer (0.067 mol/l) of pH 6.9 at 37 °C. Mass loss and water uptake were determined by weighing the samples before and after drying to constant weight *in vacuo* at 40 °C.

In vivo study

Bone plates and screws

Bone plates with dimensions of 26.0×7.0×2.0 mm and screws with a length of 8.0 mm, a core diameter of 2.0 mm and an outer diameter of 2.7 mm were used (Fig. 2). Before implantation, the implants were disinfected in 0.5 % chlorhexidine in 70 % ethanol and in a Cidex solution (containing glutaraldehyde, 22.5 g/l) at room temperature for 10 min and thereafter extensively rinsed with a sterile 0.9 % saline solution.

Load at fracture of the PDLLA/P(TMC-CL) bone plates was measured on an Instron 4301 tensile tester immediately after disinfection and before implantation, and at 6 and 12 weeks. Explanted bone plates and screws (at 6, 12 and 18 weeks postoperatively) were examined with differential scanning calorimetry (DSC) on a Perkin Elmer DSC-7. Samples (5-10 mg) were heated at a scanning rate of 10 °C/min. Gel permeation chromatography (GPC) was performed in chloroform or tetrahydrofuran relative to narrow polystyrene standards. Water uptake of the explanted devices was measured by weighing before and after drying to constant weight *in vacuo* at 40 °C. Scanning electron micrographs (SEM) of the dried devices were made on an ISI-DS-130 microscope after sputter coating with gold.

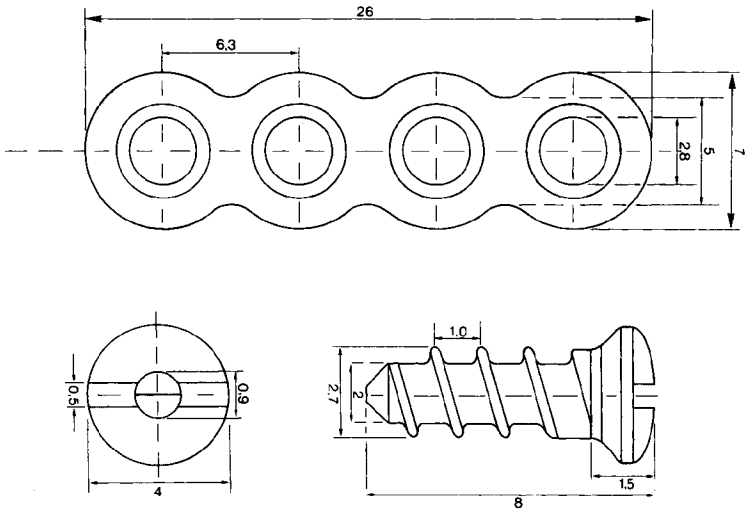

Figure 2 Dimensions of the PDLLA/P(TMC-CL) bone plate and screw (mm).

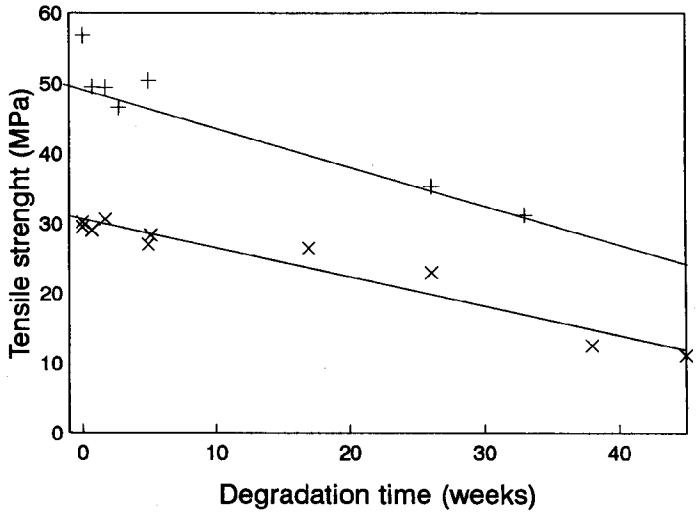

Figure 3 Tensile strength as a function of the hydrolytic degradation time of poly(85L/15D-lactide) (+) and rubber toughened poly(85L/15D-lactide) (×).

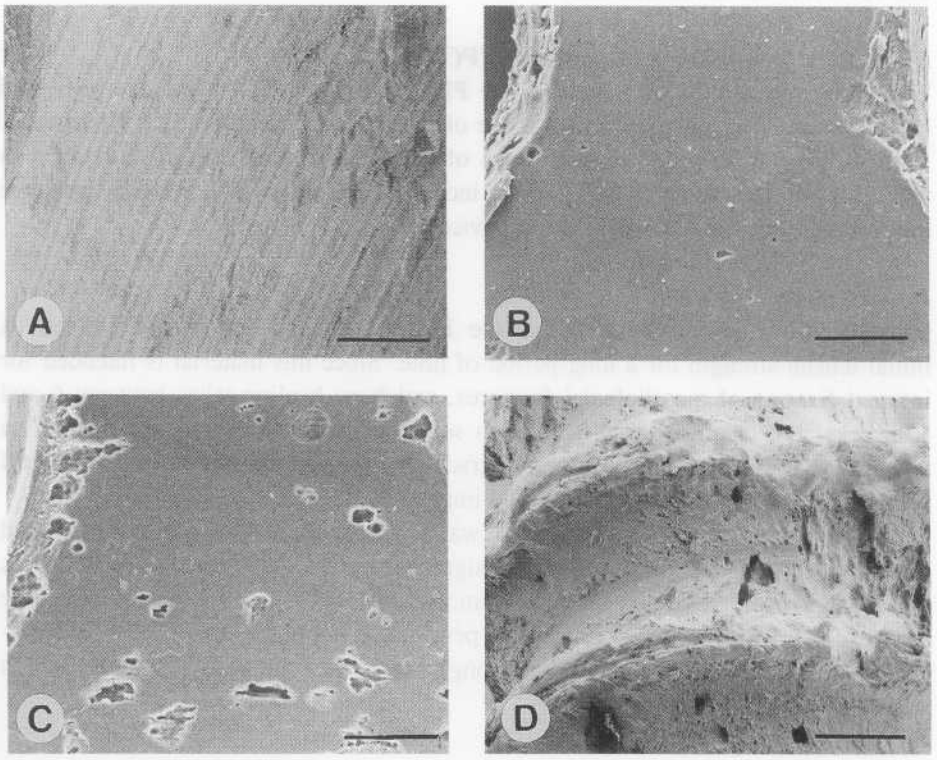

Figure 4 Scanning electron micrograph of the implants: **(A)** before implantation and **(B)** at 6, **(C)** 12 and **(D)** 18 weeks. On the surface of the explanted materials some porous structures are visible, increasing in diameter from 6 to 18 weeks. No such defects could be observed on the implants before implantation. Bar — 500 μm.

Animal pilot study

Three mongrel dogs (35-37 kg, 6 years of age) were operated on according to the procedure described by Rozema et al.[15] The dogs were allowed to use a soft diet directly postoperatively. Clinical and radiological follow-up was done at 2, 4, 6, 8, 10, 12 and 18 weeks. Under sedation, the healing process at the operation site was extra- and intraorally examined and body weight checked. Radiological follow-up consisted of oblique lateral radiographs. The dogs were killed after 6, 12 and 18 weeks.

The resected part of the mandible was fixed in 4 % formaldehyde. For light microscopic evaluation, the parts were decalcified and embedded in polyester resin. Sections of 3 μm were stained with toluidine blue.

RESULTS AND DISCUSSION

Mechanical properties of the PDLLA/P(TMC-CL) blend

The initial mechanical properties of the PDLLA/P(TMC-CL) blend are presented in Table 1 and are compared with those of the unmodified poly(85L/15D-lactide). Most striking is the enormous increase of the Izod notched impact strength to a value of 520 J/m upon blending. This increased toughness will strongly enhance the reliability of the fracture fixation device.

In vitro study

From Figure 3 it can be seen that the PDLLA/P(TMC-CL) blend retained its initial tensile strength for a long period of time. Since this material is intended for internal fixation of maxillofacial fractures, and bone healing takes between 6 and 12 weeks, the tensile strength retention seems to be sufficient for application *in vivo*. Even up to 17 weeks *in vitro* degradation, the Dynstat specimens were still very tough and showed no break in the impact test.

Up to 45 weeks, the amount of water absorbed by the degrading blend remained very low (2.5 wt%) and no significant mass loss was observed. It has previously been established that amorphous lactide copolymers degrade completely in 2.5 years.[16] Whether this period also holds for the PDLLA/P(TMC-CL) blend, has to be established in a long term *in vitro* degradation study, which is now in progress.

In vivo study

Bone plates and screws

The initial load at fracture of the plates averaged 200 N and did not change during the follow-up period, which agrees with the *in vitro* results. The PDLLA/P(TMC-CL) implants preserved their mechanical properties for a longer period than needed for normal bone healing of mandibular fractures.

In previous studies on the degradation of PLLA, no differences in mass loss, water uptake and change in molecular weight between *in vivo* and *in vitro* studies were observed.[2] Indeed, for the *in vivo* degraded implants we found similar results for the amount of absorbed water and mass loss as were determined *in vitro*. After 18 weeks, the molecular weight ($\overline{M}_n$) of the explanted material had decreased from 210 to 102.

SEM analysis of the surfaces of the explanted materials revealed some porous structures increasing in diameter from 6 to 18 weeks. No such structures were observed on the implants before implantation and might be attributed to a leaching process of the rubber from the surface of the implants (Fig. 4).

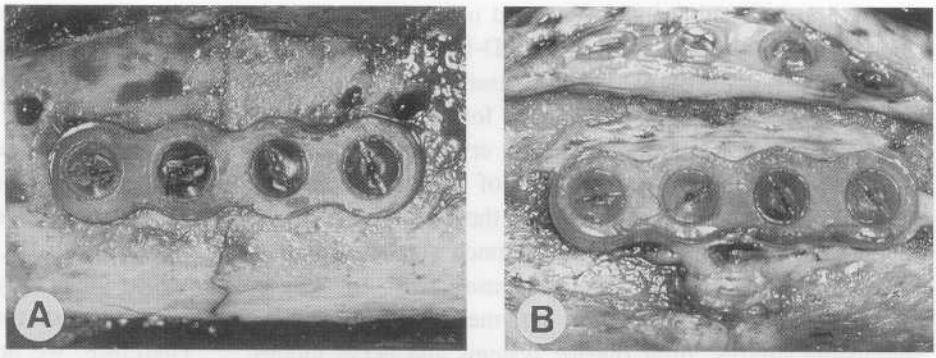

Figure 5 (A) Fixation of the fracture with a four-hole PDLLA/P(TMC-CL) bone plate. **(B)** Photograph of the fracture site 6 weeks postoperatively. The bone plate and screws are still intact.

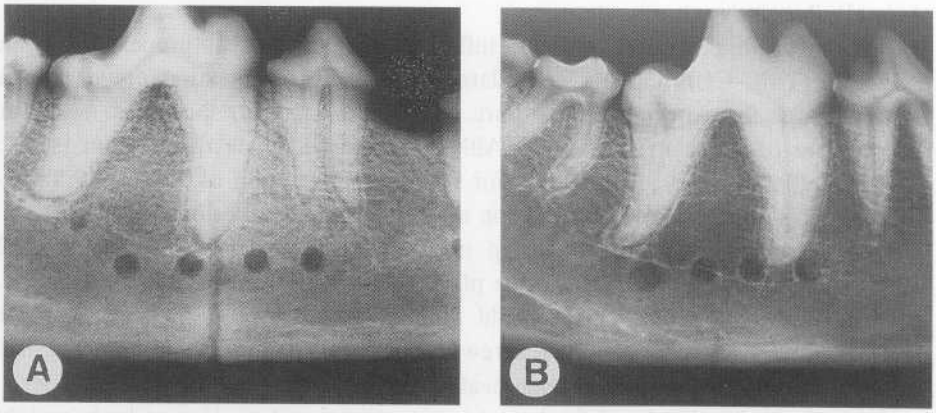

Figure 6 Lateral radiographs of the fracture site. **(A)** At 6 weeks good repositioning of the fragments and no dislocation can be observed. **(B)** At 18 weeks the fracture line has faded.

Table 1 Mechanical properties of compression moulded poly(85L/15D-lactide) (PDLLA) and rubber toughened poly(85L/15D-lactide) (PDLLA/P(TMC-CL)).

		PDLLA	PDLLA/P(TMC-CL)
Tensile strength	(MPa)	57	30
Elongation at break	(%)	7.5	130
Bending modulus	(GPa)	4.9	2.7
Dynstat unnotched	(kJ/m^2)	4.0	No break
Izod notched	(J/m)	40	520

In vivo, no crystallinity was observed up to 18 weeks. In a previous degradation study on amorphous poly(50L/50D-lactide), which is comparable to the amorphous poly(85L/15D-lactide) used in this study, it was observed that crystalline oligomeric species can be formed after almost complete degradation.[17] The very small amount of residual crystallites had a low melting temperature (T_m = 110 °C) and a low enthalpy of fusion compared to the values found for degraded PLLA. This indicates that the crystallites formed in amorphous lactide copolymers during degradation are much smaller than the ones found in PLLA, which cause the adverse tissue response. TMC and CL are known to yield fully degradable and biocompatible polymers which have already been used for degradable sutures, drug release systems and nerve guides.[18,19] Therefore, we do not expect adverse late tissues reactions during degradation of PDLLA/P(TMC-CL) *in vivo*.

Animal pilot study

The disinfection procedure did not influence the mechanical properties of the PDLLA/P(TMC-CL) implants. Standard hospital EO-sterilization could not be used because the working temperature (52 °C) is close to the glass transition temperature of the matrix (55 °C). Although glutaraldehyde disinfection is also used for other biomedical implants, for routine implantation of PDLLA/P(TMC-CL) implants an alternative sterilization method should be developed.

No screw failure occurred during insertion of the screws. After 6 and 12 weeks, the PDLLA/P(TMC-CL) bone plates and screws were still intact (Fig. 5). After 6 weeks, the bone plate could simply be removed by unscrewing the screws. After 18 weeks, all the screws were broken and the bone plate had loosened, although undisturbed bone healing had already occurred after 12 weeks.

Postoperatively, the dogs' food intake was normal and no loss of body weight was measured. Normal postoperative bone and wound healing was seen without clinical manifestations of inflammation. On the radiographs, good repositioning of the fragments and no dislocations were seen in all dogs (Fig. 6). At 12 and 18 weeks, the fracture line had faded and no callus was visible on the radiographs. Light microscopic study revealed secondary bone healing in all dogs. At 6 weeks, the fracture gap was filled with newly formed cancellous bone. At 18 weeks, lamellar bone was deposited in the interfragmentary space. In one dog some periosteal and some more endosteal callus and small areas with fibrocartilage were visible (Fig. 7), indicating some fracture mobility during the bone healing period. In the other dogs only a small amount of endosteal callus was observed. The bone plate was covered by a thin fibrous capsule without signs of an inflammatory or a foreign-body reaction. After 12 and 18 weeks, the capsule had thickened and showed a more mature image. Although tensile strength and bending modulus of the PDLLA/P(TMC-CL) devices were lower than those of

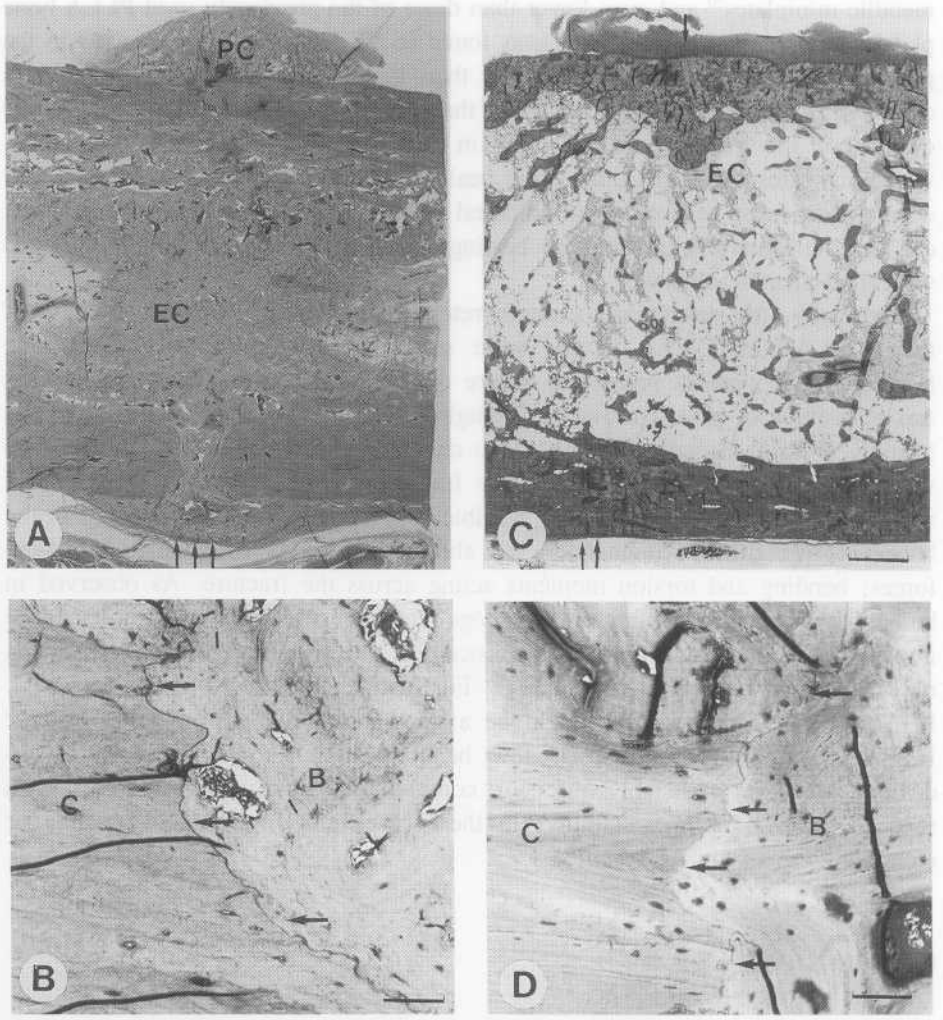

Figure 7 Photomicrographs of a horizontal section of the cortex of the fractured site. **(A)** At 6 weeks some periosteal (PC) and endosteal callus (EC) is visible (bar — 200 μm). **(B)** The demarcation line (arrows) and the original cortex (C) can be seen. The interfragmentary space is filled with newly formed cancellous bone (B) (bar — 2.5 μm). **(C)** At 18 weeks only some endosteal callus can be detected (EC). The fracture is pointed out by the arrows (bar — 200 μm). **(D)** The demarcation line (arrows) and the original cortex (C) can be seen. Lamellar bone (B) is visible in the interfragmentary space (bar — 2.5 μm).

metallic miniplates[20] and even lower than those of the previously used PLLA bone plates[2,3] undisturbed bone healing was found in all dogs. The devices used in the present study had smaller dimensions than the as-polymerized PLLA devices applied in previous studies. Although the mechanical properties seemed to be quite poor for fracture fixation, only in one dog was periosteal callus found, which indicates that during the bone healing period some fracture mobility had occurred. It must be noted that endosteal callus, as observed in the other dogs, can also be found during the bone healing period of mandibular fractures treated with rigid metallic devices.[21]

Especially, the mechanical strength retention and the high-impact strength of the PDLLA/P(TMC-CL) devices were sufficient to enable undisturbed bone healing and to prevent premature failure of the devices. Fracture characteristics and magnitude of postoperative loads might also have favoured undisturbed bone healing. With a specially designed bone clamp a single fracture of the mandible was made.[15] No additional loss of bone fragments was observed and anatomical repositioning of the fragments was possible in all dogs. The serrated edges in the buccal cortex of the fragments were able to neutralize components of shear forces, bending and torsion moments acting across the fracture. As observed in humans with mandibular fractures, in dogs bite forces might have been decreased immediately postoperatively by proprioceptive mechanisms, which resulted in reduced loads on the bone plates.[22] For single fractures of the mandible, PDLLA/P(TMC-CL) devices might be a good alternative for metallic devices. However, with respect to their low bending modulus, PDLLA/P(TMC-CL) devices are not predictably safe for complex or comminuted fractures with reduced interfragmentary stability. In these cases more rigid biodegradable or metallic devices should be applied.

CONCLUSIONS

In vitro, the PDLLA/P(TMC-CL) blend retained its tensile and impact strength for a sufficiently long period to make it suitable for application as a fracture fixation device for less loaded cranio-maxillofacial fractures and osteotomies. These expectations have been confirmed by the results of the animal pilot study. Based on these promising results, a more extensive animal study will be performed.

In vitro, up to 45 weeks, mass loss and water uptake were negligible. Long-term degradation studies are necessary to gain insight into the ultimate degradation pattern of the PDLLA/P(TMC-CL) blend.

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